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Evans−Tishchenko Coupling of Heteroaryl Aldehydes

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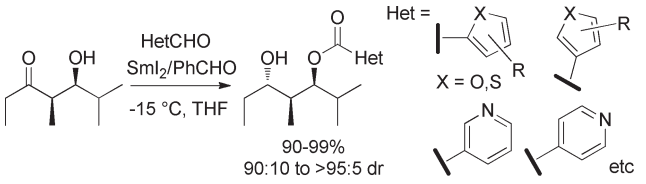

The low-temperature Evans−Tishchenko coupling of a range of functionalized heteroaryl aldehydes with β-hydroxy ketones in the presence of a Sm(III) catalyst has been achieved with high yields (90−99%) and good to excellent diastereoselectivity (90:10 → 95:5 dr). However, at room temperature a retro-aldol aldol-Tishchenko reaction was found to compete with the desired Evans−Tishchenko reaction. Identification of these byproducts has allowed the corresponding aldol-Tishchenko reaction to be optimized for several heteroaryl aldehydes.

The Evans−Tishchenko reaction[1] has proved to be a highly successful method for coupling aliphatic aldehydes with complex, multifunctional β-hydroxy ketones and enones to generate 1,3-*anti* diol monoesters in excellent yield and diastereoselectivity. It has played a pivotal role in the synthesis of many natural products,[2] and has also been used for the mild oxidation of aldehydes to carboxylic acids.[3] The presence of heteroaryl ester moieties in a range of complex natural products such as the oxazole esters found in the tubulin-disrupting disorazoles[4] and theonezolide A,[5] and the thiazole esters found in the potent actin-disrupting lyngbyabellins and hectochlorins,[6] suggests that a heteroaryl Evans−Tishchenko reaction might provide a powerful new method for the selective introduction of a range of heteroaryl esters for use in the synthesis of analogues of these intruiging natural products (Figure 1). Indeed, in pursuit of a novel synthetic route toward heteroaryl analogues of the disorazoles,[7] we identified the development of a heteroaryl Evans−Tishchenko reaction as a key step.

Evans and Hoveyda first demonstrated the high-yielding coupling of aliphatic aldehydes to β-hydroxy ketones in the presence of a samarium catalyst in 1990.[1] The active catalytic species is presumed to be a samarium(III) pinacol adduct $[(RCHO)_2SmI\cdot SmI_3]$ **2** generated in situ from an aldehyde (RCHO) and samarium diiodide through a radical coupling process. A chairlike transition state accounts for the high diastereoselectivity (> 95:5) typically observed in these reactions (Scheme 1). Although it has been demonstrated that a limited range of other species also may be used to catalyze the Evans−Tishchenko reaction including Cp_2ZrH_2,[8] $Sc(OTf)_3$,[9] and $Ti(O^iPr)_4$,[10] these have not found widespread use in synthesis. Instead for aliphatic aldehydes and benzaldehyde, the use of samarium diiodide has prevailed. This is due both to the relative ease of formation of the samarium diiodide based reagent and the rapid reaction times which it embues (typically 20 min−1 h). However, there are potential drawbacks with the use of samarium diiodide in the presence of heteroaryl aldehydes. Fang has reported a complex mixture of pinacol-coupled, carbonyl-coupled, and trimeric products when 3-thiophenecarboxaldehyde was treated with samarium diiodide.[11] Furthermore, when 2-thiophenecarboxaldehyde was treated with samarium diiodide, the pinacol-coupled adduct was not observed at all.[11a] However, Raimondi has demonstrated that upon the addition of $Ti(O^iPr)_4$ the 2-thiophenecarboxaldehyde pinacol adduct may be recovered in trace amounts.[12] In contrast, the corresponding 2-furancarboxaldehyde undergoes pinacol coupling in moderate yield when treated with samarium diiodide.[12] This precedent led us to conclude that it would be necessary to pursue both an in situ catalyst generation route, using the heteroaryl aldehyde, and also Sm(III) pinacol catalyst formation using benzaldehyde or a similar sacrificial aldehyde.

The β-hydroxy ketone **3** was chosen for this study due to its ready preparation from commercially available starting

(1) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.
(2) For recent examples, see: (a) Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567. (b) Smith, A. B. III; Cox, J. M.; Furuichi, N.; Kenesky, C. S.; Zheng, J.; Atasoylu, O.; Wuest, W. M. *Org. Lett.* **2008**, *10*, 5501. (c) Paterson, I.; Razzak, M.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 3295. (d) Lanners, S.; Norouzi-Arasi, H.; Salom-Roig, X. J.; Hanquet, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 7086. (e) Aird, J. I.; Hulme, A. N.; White, J. W. *Org. Lett.* **2007**, *9*, 631. (f) For a notable example of the coupling of a saturated heterocyclic aldehyde, see: Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906.
(3) (a) Smith, A. B., III; Lee, D. *J. Am. Chem. Soc.* **2007**, *129*, 10957. (b) Smith, A. B., III; Adams, C. M.; Barbosa, S. A. L. *J. Am. Chem. Soc.* **2003**, *125*, 350. (c) Smith, A. B., III; Lee, D.; Adams, C. M.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 4539.
(4) Jansen, R.; Irschik, H.; Reichenbach, H.; Wray, V.; Höfle, G. *Liebigs Ann. Chem.* **1994**, 759.
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(7) For other synthetic approaches to the disorazoles, see: (a) Schackel, R.; Hinkelmann, B.; Sasse, F.; Kalesse, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1619. (b) Hopkins, C. D.; Wipf, P. *Nat. Prod. Rep.* **2009**, *26*, 585.
(8) Umekawa, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 3409.
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(10) Delas, C.; Blacque, O.; Moïse, C. *Tetrahedron Lett.* **2000**, *41*, 8269.
(11) (a) Yang, S.-M.; Fang, J.-M. *J. Org. Chem.* **1999**, *64*, 394. (b) Yang, S. M.; Fang, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2669.
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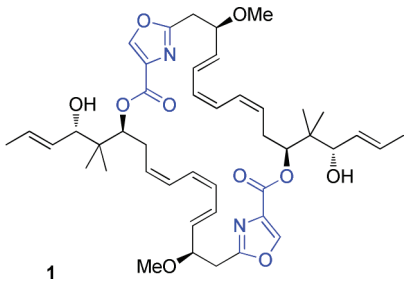
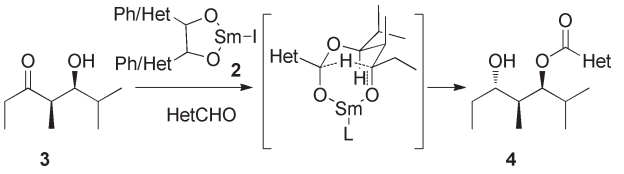


FIGURE 1. Heteroaryl ester containing mixed polyketide/nonribosomal peptide derived natural product, disorazole C_1 **1**.

SCHEME 1. Evans−Tishchenko Coupling, Using a Sm(III) Catalyst [$L_2SmI \cdot SmI_3$] 2 Generated Either (i) in Situ from the Heteroaryl Aldehyde (HetCHO) or (ii) Pre-formed Using Benzaldehyde



materials on multigram scale via an aldol reaction (dr *syn*:*anti* > 95:5).[13] Evans has determined that a range of relative α,*β*-stereochemistries may be used in the Evans−Tishchenko reaction.[1] However, the inclusion of an α-chiral center, and in particular one with a *syn* stereorelationship, could provide an important mechanistic indicator for this reaction (vide infra). In light of the potential for the generation of unwanted side products in the reaction of heteroaryl aldehydes, we chose to use a rather low catalyst loading (5 mol % rather than a more typical 20−30 mol %) for these studies. Thus an excess of the heteroaryl aldehyde (4.0 equiv) was treated with 10 mol % SmI_2, generating 5 mol % of the catalyst in situ. The *β*-hydroxy ketone **3** was added to the resultant pinacol adduct catalyst **2** and excess aldehyde, and the reaction was quenched after 1 h to give the 1,3-*anti* diol monoester **4**.

At room temperature, electron-poor heteroaryl aldehydes 4-pyridinecarboxaldehyde (Table 1, entry 1) and 3-pyridinecarboxaldehyde (Table 1, entry 3) undergo Evans−Tishchenko coupling to generate the corresponding 1,3-*anti* diol monoesters **4a** and **4b** with excellent yield and diastereoselectivity.[14] Furthermore, when the catalytic loading was reduced to 2 mol % on a multigram scale for 4-pyridinecarboxaldehyde, the yields of **4a** and diastereoselectivity were not compromised. Although 2-pyridinecarboxaldehyde (Table 1, entry 5) coupled to produce **4c** as the sole isolable product, it was only in a very poor yield. These results were mirrored by those generated through preformation of the pinacol adduct catalyst using benzaldehyde (Table 1, entries 2, 4, and 6). Unfortunately, electron-rich heteroaryl aldehydes 3-furancarboxaldehyde, 2-furancarboxaldehyde, 3-thiophenecarboxaldehyde, and 2-thiophenecarboxaldehyde (Table 1, entries 7−14) all generated a mixture of products, with poor to

TABLE 1. Room Temperature Evans−Tishchenko Coupling Reactions of Heteroaryl Aldehydes (HetCHO)

entry	aldehyde	method[d]	product	% yield (dr)[a]
1	4-pyridinecarboxaldehyde	A	**4a**	99 (90:10)
2	4-pyridinecarboxaldehyde	B	**4a**	93 (91:09)
3	3-pyridinecarboxaldehyde	A	**4b**	99 (96:04)
4	3-pyridinecarboxaldehyde	B	**4b**	99 (95:05)
5	2-pyridinecarboxaldehyde	A	**4c**	11 (n.d.)[b]
6	2-pyridinecarboxaldehyde	B	**4c**	13 (n.d.)[b]
7	3-furancarboxaldehyde	A	**4d**	63[c] (89:11)
8	3-furancarboxaldehyde	B	**4d**	62[c] (90:10)
9	2-furancarboxaldehyde	A	**4e**	69[c] (92:08)
10	2-furancarboxaldehyde	B	**4e**	12[c] (92:08)
11	3-thiophenecarboxaldehyde	A	**4f**	61[c] (90:10)
12	3-thiophenecarboxaldehyde	B	**4f**	23[c] (89:11)
13	2-thiophenecarboxaldehyde	A	**4g**	47[c] (89:11)
14	2-thiophenecarboxaldehyde	B	**4g**	39[c] (90:10)

[a]Diastereomeric ratio determined by HPLC and/or NMR analysis. [b]Not determined. [c]Conversion as assessed by HPLC. [d]Method A: (i) SmI_2 (0.1 equiv), HetCHO (4.0 equiv), THF, rt, 30 min; (ii) **3** (1.0 equiv), rt, 1 h. Method B: (i) SmI_2 (0.1 equiv), PhCHO (0.1 equiv), THF, rt, 30 min; (ii) HetCHO (4.0 equiv), **3** (1.0 equiv), rt, 1 h.

moderate yields of the desired 1,3-*anti* diol monoester **4d**−**g**. In each case the remainder of the mass balance was accounted for by two distinct byproducts.

In an attempt to reduce formation of the unwanted byproducts alongside esters **4d**−**g**, we investigated the use of low-temperature Evans−Tishchenko conditions. The aldehyde 2-furancarboxaldehyde was subjected to Evans−Tishchenko conditions using 30 mol % Sm(III) at reduced temperatures (−15, −40, and −78 °C) for 1 h. At these low temperatures we found that turnover of the samarium catalyst was sluggish, but stoichiometric yields of product with respect to catalytic loading could be obtained and crucially no byproduct formation was observed. In the presence of 1 equiv of the Sm(III) species the desired *anti*-diol monoester **4d** was obtained in high yield (> 95%) and with excellent diastereoselectivity (> 95:5). Furthermore, these conditions proved to be robust across a range of additional functionalities on the furan or thiophene ring (Table 2, entries 9−12) and even for benzo[*b*]thiophene-3-carboxaldehyde and *N*-Boc-indole-3-carboxaldehyde (Table 2, entries 13 and 14). Significantly, however, aldehydes possessing an α-chelating heteroatom (e.g., 2-pyridinecarboxaldehyde, 2-methyl-oxazole-4-carboxaldehyde), or where hemiacetal formation (the first step of the Evans−Tishchenko reaction pathway) was disfavored upon coordination of the Sm(III) catalyst to the heteroaryl substrate (e.g., indole-3-carboxaldehyde in the absence of Boc-protection, or pyrrole-2-carboxaldehyde), did not give good yields of the desired Evans−Tishchenko products.

Monitoring the formation of products **4d**−**g** over time at room temperature led us to conclude that byproduct formation did not result from product decomposition. Analysis of the spectroscopic data suggested that at temperatures greater than −15 °C a secondary pathway competes with the desired Evans−Tishchenko coupling, namely a retro-aldol aldol-Tishchenko (RAAT) coupling (Scheme 2).[15] This is probably due to the comparatively slow reaction rate of electron-rich heteroaryl aldehydes in the Evans−Tishchenko reaction by

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(14) The relative stereochemistry of the major and minor diasteremomers was confirmed through separation by HPLC, hydrolysis to give the corresponding diols, and spectroscopic comparison with literature data and authentic samples.

(15) A similar dissociation−recombination process has been demonstrated using a crossover experiment for the Evans−Tishchenko reaction of the aldol adduct of 3-pentanone/deuteriated-benzaldehyde with benzaldehyde: Lu, L.; Chang, H. Y.; Fang, J.-M. *J. Org. Chem.* **1999**, *64*, 843.

TABLE 2. Low-Temperature Evans−Tishchenko Coupling Reactions of Heteroaryl Aldehydes (HetCHO)

entry	aldehyde	method[b]	product	% yield (dr)[a]
1	3-furancarboxaldehyde	C	**4d**	99 (>95:5)
2	3-furancarboxaldehyde	D	**4d**	98 (>95:5)
3	2-furancarboxaldehyde	C	**4e**	98 (>95:5)
4	2-furancarboxaldehyde	D	**4e**	99 (91:09)
5	3-thiophenecarboxaldehyde	C	**4f**	99 (>95:5)
6	3-thiophenecarboxaldehyde	D	**4f**	99 (>95:5)
7	2-thiophenecarboxaldehyde	C	**4g**	99 (>95:5)
8	2-thiophenecarboxaldehyde	D	**4g**	99 (91:09)
9	5-phenylfuran-2-carboxaldehyde	D	**4h**	92 (>95:5)
10	5-nitrofuran-2-carboxaldehyde	D	**4i**	93 (>95:5)
11	5-bromofuran-2-carboxaldehyde	D	**4j**	90 (94:6)
12	5-bromothiophene-2-carboxaldehyde	D	**4k**	99 (>95:5)
13	benzo[*b*]thiophene-3-carboxaldehyde	D	**4l**	95 (92:8)
14	*N*-Boc-indole-3-carboxaldehyde	D	**4m**	90 (90:10)

[a]Diastereomeric ratio determined by HPLC and/or NMR analysis. [b]Method C: (i) SmI_2 (2.0 equiv), HetCHO (4.0 equiv), THF, rt, 30 min; (ii) **3** (1.0 equiv), −15 °C, 1 h. Method D: (i) SmI_2 (2.0 equiv), PhCHO (2.0 equiv), THF, rt, 30 min; (ii) HetCHO (4.0 equiv), **3** (1.0 equiv), THF, −15 °C, 1 h.

SCHEME 2. Retro-Aldol Aldol-Tishchenko (RAAT) Reactions of β-Hydroxy Ketone 3

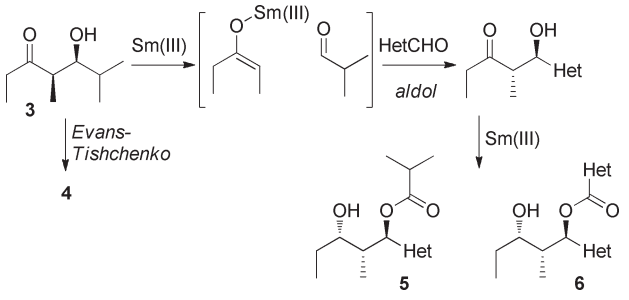
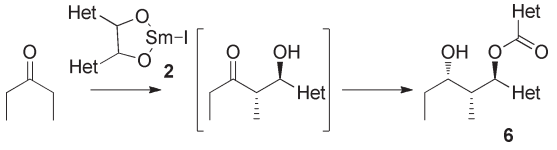


TABLE 3. Aldol-Tishchenko Reactions of 3-Pentanone with Heteroaryl Aldehydes.[a]



entry	aldehyde	product	% yield
1	3-furancarboxaldehyde	**6d**	68
2	3-thiophenecarboxaldehyde	**6f**	61
3	2-thiophenecarboxaldehyde	**6g**	63

[a]Reagents and conditions: (i) SmI_2 (0.6 equiv), HetCHO (4.0 equiv), THF, rt, 1 h; (ii) 3-pentanone (1.0 equiv), 0 °C, 1 h..

comparison with their electron-poor counterparts.[16] The samarium enolate formed in competition undergoes an aldol addition with the excess heteroaryl aldehyde to give the thermodynamically favored *anti* aldol diastereomer,[17] followed by Evans−Tishchenko coupling with either the displaced isobutyraldehyde or an additional equivalent of the heteroaryl aldehyde, to give RAAT products **5** and **6**, respectively.

The aldol-Tishchenko reaction has been extensively studied,[17] and recent interest has focused on the development of direct asymmetric aldol-Tishchenko reactions.[18] While a limited number of heteroaryl aldehydes have been used in previous studies in conjunction with propiophenone derivatives or acyl silanes,[18c,d] the reaction of heteroaryl aldehydes with aliphatic ketones such as 3-pentanone has not previously been reported. Thus we developed a simple protocol for the synthesis of aldol-Tishchenko adducts from 3-pentanone and the heteroaryl aldehyde using a Sm(III) catalyst generated in situ (Table 3); adducts **6** were obtained as a single diastereomer.[19]

In conclusion, we have demonstrated that Evans−Tishchenko coupling is successful in the presence of electron-poor heteroaryl aldehydes at room temperature with low catalyst loadings, and also with electron-rich heteroaryl aldehydes at low temperature, albeit it requiring a stoichiometric loading of the Sm(III) catalyst. We believe that with the continued emergence of new PKS-NRPS hybrid natural products,[20] and the unrivalled potential of natural product frameworks as drug leads,[21] that this heteroaryl variant of the Evans−Tishchenko reaction will find use in the synthesis of hybrid analogues. Indeed, its application to the synthesis of analogues of the tubulin-disruptor disorazole C_1 is currently under investigation in our laboratories.

Experimental Section

Method A. Heteroaryl aldehyde (4.00 mmol) was added to samarium diiodide (10.0 mL, 0.100 mmol, 0.010 M in THF) at rt and the resultant yellow solution was stirred for 30 min. The β-hydroxy ketone **3** (0.158 g, 1.00 mmol) was added and the reaction mixture was stirred for 1 h. The reaction was quenched with potassium sodium tartrate (50 mL, sat. aq.), extracted with DCM (3 × 20 mL), washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography and HPLC.

Method D. Benzaldehyde (0.202 mL, 2.00 mmol) was added to samarium diiodide (2.00 mmol) in THF (10 mL) at rt and the

(16) We have observed similar competing side reactions in conducting intramolecular Evans−Tishchenko reactions to form 8-membered rings: Hulme, A. N.; Howells, G. E. *Tetrahedron Lett.* **1997**, *38*, 8245.

(17) For reviews of the aldol-Tishchenko reaction, see: (a) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1. (b) Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 557. (c) Mlynarski, J. *Eur. J. Org. Chem.* **2006**, 4779.

(18) For representative examples, see: (a) Rohr, K.; Herre, R.; Mahrwald, R. *J. Org. Chem.* **2009**, *74*, 3744. (b) Stodulski, M.; Jaźwiński, J.; Mlynarski, J. *Eur. J. Org. Chem.* **2008**, 5553. (c) Honda, M.; Iwamoto, R.; Nogami, Y.; Segi, M. *Chem. Lett.* **2005**, *34*, 466. (d) Gnanadesikan, V.; Horiuchi, Y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7782.

(19) Stereochemistry was assigned as the 1,2-*anti* aldol adduct with a 1,3-*anti* diol monoester on the basis of literature precedent (refs 15 and 17).

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(21) (a) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461. (b) Paterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451.

resultant yellow solution was stirred for 30 min. The reaction mixture was cooled to −15 °C and heteroaryl aldehyde (4.00 mmol) was added, followed by β-hydroxy ketone **3** (0.158 g, 1.00 mmol), and the reaction mixture was stirred for 1 h. The reaction was quenched with potassium sodium tartrate (50 mL, sat. aq.), extracted with DCM (3 × 20 mL), washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography and HPLC.

Isonicotinic acid (1*SR*,2*SR*,3*SR*)-3-hydroxy-1-isopropyl-2-methylpentyl ester 4a (method A: 262 mg, 99%): HPLC R_t (hexane:EtOAc, 50:50) 18.4; IR (neat, cm^{-1}) 3421, 1728; ^1H NMR δ (250 MHz, $CDCl_3$) 8.75 (2H, br s), 7.81 (2H, d, J = 6.0), 5.13 (1H, dd, J = 9.5, 1.5), 3.07 (1H, br s), 3.00 (1H, td, J = 8.5, 2.5), 2.04 (1H, dsept, J = 9.5, 6.6), 1.79 (1H, dqd, J = 8.5, 7.0, 1.5), 1.70−1.51 (1H, m), 1.38−1.20 (1H, m), 0.92−0.85 (12H, m); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 166.5 (C), 151.1 (CH), 137.6 (C), 123.4 (CH), 81.6 (CH), 73.6 (CH), 40.7 (CH), 30.2 (CH), 27.2 (CH_2), 20.1 (CH_3), 19.3 (CH_3), 10.3 (CH_3), 10.1 (CH_3); m/z (ESI+, MeOH) 288 ($[M + Na]^+$, 34%), 266 ($[M + H]^+$, 100); HRMS (FAB, 3-NOBA) $[M + H]^+$ found 266.1751, $C_{15}H_{24}NO_3$, requires 266.1756.

Nicotinic acid (1*SR*,2*SR*,3*SR*)-3-hydroxy-1-isopropyl-2-methylpentyl ester 4b (method A: 262 mg, 99%): HPLC R_t (hexane; EtOAc, 50:50) 19.5; IR (neat, cm^{-1}) 3423, 1718; ^1H NMR δ (250 MHz, $CDCl_3$) 9.25 (1H, d, J = 1.6), 8.80 (1H, dd, J = 4.8, 1.4), 8.31 (1H, dt, J = 8.0, 1.9), 7.40 (1H, ddd, J = 8.0, 4.8, 0.7), 5.17 (1H, dd, J = 9.6, 1.8), 3.27 (1H, br s), 3.08−2.98 (1H, td, J = 8.6, 2.7), 2.04 (1H, dsept, J = 9.6, 6.6), 1.82 (dqd, J = 8.7, 6.9, 1.8), 1.64 (1H, dqd, J = 14.1, 7.3, 2.7), 1.30 (1H, ddq, J = 14.1, 8.4, 7.3), 0.90 (3H, d, J = 6.7), 0.89 (3H, t, J = 7.3), 0.88 (3H, d, J = 6.5), 0.86 (3H, d, J = 6.9); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 166.7 (C), 153.9 (CH), 151.3 (CH), 137.8 (CH), 126.3 (C), 123.8 (CH), 81.2 (CH), 73.6 (CH), 40.7 (CH), 30.2 (CH), 27.2 (CH_2), 20.2 (CH_3), 19.2 (CH_3), 10.2 (CH_3), 10.1 (CH_3); m/z (ESI+, MeOH) 553 ($[2M + Na]^+$, 100%), 288 ($[M + Na]^+$, 29), 266 ($[M + H]^+$, 58); HRMS (ESI+, MeOH) $[M + H]^+$ found 266.1753, $C_{15}H_{24}NO_3$, requires 266.1751.

Furan-3-carboxylic acid (1*SR*,2*SR*,3*SR*)-3-hydroxy-1-isopropyl-2-methylpentyl ester 4d (method D: 250 mg, 98%): HPLC R_t (hexane:EtOAc, 80:20) 13.2; IR (neat, cm^{-1}) 3518, 1703; ^1H NMR δ (500 MHz, $CDCl_3$ 8.07−8.05 (1H, m), 7.47 (1H, t, J = 1.7), 6.78−6.77 (1H, m), 5.06 (1H, dd, J = 9.8, 1.7), 3.51 (1H, br s), 3.09 (1H, td, J = 8.4, 2.4), 1.95 (1H, dsept, J = 9.8, 6.7), 1.71 (1H, dqd, J = 8.9, 7.0, 1.7), 1.59 (1H, dqd, J = 14.0, 6.5, 2.8), 1.30 (1H, ddq, J = 14.0, 8.3, 7.2), 0.90 (3H, t, J = 7.4), 0.87 (3H, d, J = 6.4), 0.86 (3H, d, J = 7.0), 0.80 (3H, d, J = 6.9); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 164.9 (C), 148.3 (CH), 144.2 (CH), 119.5 (C), 110.3 (CH), 80.0 (CH), 73.4 (CH), 40.7 (CH), 30.1 (CH), 27.2 (CH_2), 20.2 (CH_3), 19.2 (CH_3), 10.3 (CH_3), 9.9 (CH_3); m/z (ESI+, MeOH) 531 ($[2M + Na]^+$, 12%), 277 ($[M + Na]^+$, 12); HRMS (ESI+, 3-NOBA) $[M + H]^+$ found 255.1595, $C_{14}H_{23}O_4$, requires 255.1596.

Furan-2-carboxylic acid (1*SR*,2*SR*,3*SR*)-3-hydroxy-1-isopropyl-2-methylpentyl ester 4e (method D: 254 mg, 99%): HPLC R_t (Hex:EtOAc, 80:20) 14.8; IR (neat, cm^{-1}) 3501, 1715; ^1H NMR δ (250 MHz, $CDCl_3$) 7.61−7.60 (1H, m), 7.21−7.20 (1H, m), 6.53−6.52 (1H, m), 5.09 (1H, dd, J = 9.7, 1.7), 3.09 (1H, td, J = 8.6, 2.6), 2.00 (1H, dsept, J = 9.7, 6.8), 1.74 (1H, dqd, J = 8.6, 7.1, 1.8), 1.60 (1H, dqd, J = 14.0, 7.6, 2.8), 1.50 (1H, br s), 1.30 (1H, ddq, J = 14.0, 8.4, 7.3), 0.96−0.94 (9H, m), 0.89 (3H, d, J = 6.9); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 160.1 (C), 146.8 (CH), 144.4 (C), 118.4 (CH), 112.0 (CH), 80.5 (CH), 73.1 (CH), 40.4 (CH), 29.8 (CH), 26.8 (CH_2), 19.9 (CH_3), 18.9 (CH_3), 10.0 (CH_3), 9.6 (CH_3); m/z (ESI+, MeOH) 531 ($[2M + Na]^+$, 100%), 277 ($[M + Na]^+$, 24); HRMS (ESI+, 3-NOBA) $[M + H]^+$ found 255.1602, $C_{14}H_{23}O_4$, requires 255.1596.

Thiophene-3-carboxylic acid (1*SR*,2*SR*,3*SR*)-3-hydroxy-1-isopropyl-2-methylpentyl ester 4f (method D: 270 mg, 99%): HPLC R_t (hexane:EtOAc, 80:20) 12.5; IR (neat, cm^{-1}) 3498, 1693, 1649, 1522; ^1H NMR δ (500 MHz, $CDCl_3$ 8.17 (1H, dd, J = 3.0, 1.2), 7.56 (1H, td, J = 5.0, 1.1), 7.36 (1H, ddd, J = 5.0, 3.0, 1.1), 5.09 (1H, dd, J = 9.6, 1.7), 3.59 (1H, br s), 3.10 (1H, td, J = 8.7, 2.7), 2.00 (1H, dsept, J = 9.6, 6.6), 1.73 (1H, dqd, J = 8.7, 7.0, 1.7), 1.59 (1H, dqd, J = 14.4, 7.3, 2.7), 1.30 (1H, ddq, J = 14.4, 8.0, 7.1), 0.99−0.95 (9H, m), 0.92 (3H, d, J = 6.9); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 164.4 (C), 133.7 (C), 133.6 (CH), 128.4 (CH), 126.6 (CH), 80.3 (CH), 73.4 (CH), 40.8 (CH), 30.2 (CH), 27.2 (CH_2), 20.3 (CH_3), 19.3 (CH_3), 10.3 (CH_3), 10.0 (CH_3); m/z (ESI+, MeOH) 563 ($[2M + Na]^+$, 100%), 293 ($[M + Na]^+$, 19); HRMS (FAB, 3-NOBA) $[M + H]^+$ found 271.1359, $C_{14}H_{23}O_3S$, requires 271.1379.

Thiophene-2-carboxylic acid (1*SR*,2*SR*,3*SR*)-3-hydroxy-1-isopropyl-2-methylpentyl ester 4g (method D: 267 mg, 99%): HPLC R_t (hexane:EtOAc, 80:20) 9.2; IR (neat, cm^{-1}) 3435, 1645, 1525; ^1H NMR δ (500 MHz, $CDCl_3$ 7.85 (1H, dd, J = 3.8, 1.2), 7.61 (1H, dd, J = 5.0, 1.2), 7.15 (1H, dd, J = 5.0, 3.8), 5.09 (1H, dd, J = 9.7, 1.7), 3.48 (1H, br s), 3.13 (1H, td, J = 8.8, 2.7), 2.00 (1H, dsept, J = 9.7, 6.6), 1.73 (1H, dqd, J = 8.8, 7.0, 1.7), 1.59 (1H, dqd, J = 14.8, 7.4, 2.7), 1.29 (1H, ddq, J = 14.3, 8.1, 6.9), 0.99−0.95 (9H, m), 0.92 (3H, d, J = 6.9); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 163.9 (C), 134.2 (CH), 133.8 (C), 133.2 (CH), 128.3 (CH), 80.9 (CH), 73.4 (CH), 40.8 (CH), 30.1 (CH), 27.2 (CH_2), 20.1 (CH_3), 19.2 (CH_3), 10.3 (CH_3), 10.0 (CH_3); m/z (ESI+, MeOH) 563 ($[2M + Na]^+$, 25%), 293 ($[M + Na]^+$, 8), 271 ($[M + H]^+$, 100); HRMS (ESI+, MeOH) $[M + H]^+$ found 271.1365, $C_{14}H_{23}O_3S$, requires 271.1362.

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Supporting Information Available: Experimental procedures for the synthesis of compounds **3**, **4c**, **4h**−**m**, and **6d**−**g** and spectroscopic data for Evans−Tishchenko minor diastereomers and RAAT products **5e**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.